Remarks

Claims 1-37 were pending in the subject application. By this Amendment, claims 1-37 have been cancelled and new claims 38-72 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 38-73 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1-5, 7-13, 15, and 16 have been objected to because they recite non-elected inventions. By this Amendment, the applicant has cancelled claims 1-5, 7-13, 15, and 16, and added claims 38-73, which recite "an interfering RNA specific for SHIP-1 mRNA". The applicant respectfully submits that new claims 38-73 are consistent with the election. Claims drawn to non-elected subject matter have been cancelled. Reconsideration and withdrawal of the objection is respectfully requested.

Support for new claims 38-40, 46, 47, 57, and 66-68 can be found, for example, at page 5, lines 1-22 and 27-34, and page 7, lines 13-34, of the subject specification and claims as originally filed. In addition, page 11, lines 19-26 and 31-34, and page 17, lines 19-33, indicate that the substance that inhibits SHIP function can be delivered to mammalian cells, such as human cells. Support for claims 41, 53, 63, and 69 can be found, for example, at page 11, lines 8-26 and 31-34, page 12, lines 1-9, page 15, lines 29-34, page 16, lines 1-18 and 31-34, and page 17, lines 1-9, of the specification and claims as originally filed. Support for claims 42, 54, 64, and 71, can be found, for example, at page 12, line 2, of the subject specification as originally filed. Support for claims 43, 55, 64, and 71, can be found, for example, at page 12, line 4, of the subject specification as originally filed. Support for claims 44, 56, 66, and 73, can be found, for example, at page 12, line 3, page 16, lines 1-18, and 31-34, and page 17, lines 6-9, of the subject specification as originally filed. Support for claims 45, 48, and 59, can be found, for example, at page 5, lines 6-13, and page 7, lines 24-27, of the specification and the claims as originally filed. Support for claims 47 and 58 can be found, for example, at page 5, lines 14-19, and page 8, lines 5-10, of the subject specification and claims as originally filed. Support for claims 50, 51, 60, and 61, can be found, for example, at page 8, lines 13-25, of the subject specification and claims as originally filed.

Claims 1 and 13 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The applicant respectfully submits that the phrase "or a combination thereof" does not render the claim indefinite. However, claims 5 and 13 have been cancelled, rendering this rejection moot. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 1-5, 7-13, 15, and 16 have been rejected under 35 U.S.C. §112, first paragraph, as lacking written description. The applicant traverses and respectfully submits that the subject specification provides a sufficient written description of the claimed invention. However, as indicated above, claims 1-5, 7-13, 15, and 16 have been cancelled and new claims 38-73 have been added.

The applicant respectfully submits that the subject specification provides a sufficient written description of the subject matter of claims 38-73. The Office Action indicates that the subject application does not indicate the distinguishing attributes identifying members of the genus comprising SHIP mRNA. Claims 38-73 recite that the interfering RNA is specific for SHIP-1 mRNA. Furthermore, claims 38, 46, and 57 recite that the interfering RNA reduces SHIP-1 expression within the recipient mammal. Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. William Kerr. As Dr. Kerr states, the subject invention involves the reduction of hematopoietic-specific SH2-containing inositol-5-phosphatase (SHIP) function. SHIP, which is also known in the art as SHIP-1, SHIP1, SHIPI, and SHIP-I was also the subject of Helgason, *et al.* (1998), Huber *et al.* (1998), Liu *et al.* (1999), Liu *et al.* (1998), US. Patent No. 6,090,621 (Kavanaugh *et al.*), PCT publication WO 9710252A1 (Rohrschneider, L.R.), and PCT publication WO 9712039A2 (Krystal, G.), which are cited at pages 2 and 3 of the subject specification. The mRNA sequences of mouse SHIP-1 and human SHIP-1 have been publicly available for some time. Dr. Kerr notes:

> The mRNA sequences of mouse SHIP-1 and human SHIP-1 have been publicly available since the late 1990s, as evidenced by Exhibits B and C (which are attached hereto), accession numbers NM_10566 and NM_005541, respectively, from the National Center for Biotechnology Information (NCBI) database. Although some nucleotide changes may have been subsequently made to update the GenBank sequences, Exhibits B and C show that the mouse and human SHIP-1 sequences were deposited in GenBank by papers published in 1996 and 1997.

Having the sequence of the target gene (SHIP-1), the applicant submits that one skilled in the art would readily envision target nucleic acid sequences with the recipient mammal's mRNA. Therefore, the applicant respectfully submits that the subject specification provides sufficient information regarding the genus of SHIP-1 mRNA. As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. "Due to nucleotide complementarity and the mechanism of RNA interference (RNAi), RNA molecules likely to interfere with expression of SHIP-1 could then be determined." Kerr Declaration, page 2, section 3.

Thus, the applicant submits that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-5, 7-13, 15, and 16 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicant respectfully traverses and submits that the claims are fully enabled by the subject specification.

As indicated above, claims 1-5, 7-13, 15, and 16 have been cancelled and new claims 38-73 have been added. Claims 38, 46, and 57 recite that an interfering RNA specific for SHIP-1 mRNA is administered to the mammal, wherein the interfering RNA reduces SHIP-1 expression within the mammal. Claims 46 and 57 recite methods for suppressing rejection of a transplant and suppressing

graft-versus-host disease, respectively. "Preventing" transplant rejection or graft-versus-host disease is not recited in the claims.

The Office Action indicates that the subject specification does not provide sufficient guidance resolving issues associated with *in vivo* delivery of oligonucleotides and treatment effects. As indicated by Dr. Kerr, RNAi has been demonstrated to facilitate gene silencing in a variety of animal models and cell culture, as reported or described in Zamore *et al.* (Exhibit D) and Svoboda *et al.* (Exhibit E), which accompany the Declaration. Furthermore, experimental results demonstrating reduction of SHIP-1 expression by RNAi *in vitro* and *in vivo* using delivery methods taught within the subject specification are described in Exhibits F, G, H, and I, which accompany Dr. Kerr's Declaration. As the Examiner is aware, the determination of enablement must be based on evidence as a whole. As indicated in MPEP § 2164.05, "A declaration or affidavit is, itself, evidence that must be considered" (emphasis in original). MPEP § 2164.05 states:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

Exhibit F shows reduction of SHIP-1 expression in embryonic stem (ES) cells *in vitro* by RNAi. ES cells that express the SHIP-1 gene were transfected with an irrelevant shRNA vector (Lane 3) or with two different shRNA vectors that produced siRNAS specific for SHIP-1 (Lanes 4 and 5). Ship-1 was detected using an anti-SHIP-1 antibody. As indicated by Dr. Kerr, "Panel A shows significant reduction of SHIP expression in primary ES cells after transfection of SHIP-1-specific shRNA vectors in the absence of selection. It would be expected that these vectors would also interfere with expression of the larger SH2-containing isoforms in differentiated hematopoietic cells." Kerr Declaration, page 3, section 5.

Exhibit G demonstrates reduction of SHIP-1 expression *in vivo* by RNAi, using techniques taught within the subject patent application. Exhibit G shows that induction of SHIP-1 deficiency *in vivo* by RNAi increases the frequency of circulating myeloid cells including cells with a myeloid suppressor cell phenotype. Mice were injected with a SHIP-1 shRNA vector complexed with the cationic lipid 1,2-dioleoyloxy-3-trimethylammonium propane (DOTAP) while two additional mice

received an irrelevant shRNA vector specific for the human LRBA gene. The design and sequence of the shRNA vector is shown in Exhibit H.

The mice that received the SHIP-1-specific shRNA vector showed significant suppression of all major SHIP isoforms in the spleen, while β-actin levels were essentially unaltered, as shown in Figure A of Exhibit G. Four different SHIP-1 specific siRNAs were screened for knockdown of SHIP-1 in the RAW264.7 mouse myeloid cell line or ES cells. SiRNAs #1 and #4 were pooled, complexed with DOTAP and injected intravenously into two separate mice. As with SHIP-1 shRNA-treated mice, there was partial suppression of SHIP-1 expression in peripheral blood mononuclear cells (PBMC) 20 hours after the treatment. Upon examining the impact on the myeloid compartment in PBMC, a significant increase in Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells) was found in the SHIP-1 siRNA treated mice, relative to the GL2 control animals, as shown in Figure B of Exhibit G. The sequences of siRNAs #1-4 and their respective target sites within the open reading frame of mouse SHIP-1 are shown in Exhibit I. As stated by Dr. Kerr, "these findings show that knockdown of SHIP-1 expression *in vivo* by RNAi is a feasible approach that can exert physiological effect even with partial knockdown of SHIP-1 expression." Kerr Declaration, page 4, section 7.

As taught at pages 11, 12, and 15-17, of the subject specification, various gene delivery vehicles can be used to deliver nucleic acids that target and reduce SHIP function according to the subject invention. For example, viral and non-viral vectors can be used, as indicated by Dr. Kerr in his Declaration, and as indicated at page 11, lines 31-34, page 12, and page16, lines 1-18 and 31-34, of the subject specification. As taught at page 11, lines 10-34, and page 12, lines 1-8, of the subject specification, polycationic molecules (such as liposomes) can be used as gene delivery vehicles to deliver genetic constructs for reduction of SHIP expression. The applicant notes that column 17 of U.S. Patent No. 6,025,198, which is cited by the Examiner in the Office Action, indicates that cationic liposomes may be used to deliver antisense oligonucleotides to inhibit expression of SHIP-2. As explained by Dr. Kerr in his Declaration, for the experiment shown in Exhibit G, SiRNAs were complexed with DOTAP and injected intravenously into mice. DOTAP has been used for gene delivery to mammalian cells *in vitro* and *in vivo* (see, for example, Porteous D.J. *et al.*, "Evidence for safety and efficacy of DOTAP cationic liposome mediated CFTR gene transfer to the nasal

epithelium of patients with cystic fibrosis", *Gene Ther.*, 1997, Mar., 4(3):210-218; Song Y.K. *et al.*, "Characterization of cationic liposome-mediated gene transfer *in vivo* by intravenous administration", *Hum. Gene Ther.*, 1997, Sept., 8(13):1585-1594).

The applicant respectfully submits that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques which are described in the specification and known to those of ordinary skill in the art, methods for reducing SHIP-1 expression using interfering RNA are fully enabled. At page 5, section 8, of the Declaration, Dr. Kerr states:

> Based on the experimental data demonstrating the ability to reduce expression of SHIP-1 *in vivo* in accordance with the teaching of the subject patent application, and the observed effects of SHIP-1 deficiency on NK cell function and GVHD in SHIP-/- transgenic mice (Examples 2-6 of the subject patent application), there is no reason to doubt that reduction of SHIP-1 function by RNA interference or other means of SHIP-1 inhibition will be of therapeutic benefit in suppressing transplant rejection and graft-versus-host disease in mammals, including humans.

The Office Action cites the Tamm *et al.* publication, which is a review article summarizing various clinical trials using oligonucleotides. The applicant respectfully submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Given the state of the art as demonstrated by the scientific publications submitted herewith, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art can target and reduce expression of SHIP-1 *in vitro* or *in vivo*, without resort to undue experimentation. Thus, the applicant respectfully submits that the subject specification enables the methods and compositions as currently claimed.

Accordingly, the applicant respectfully submits that, given the teaching of the specification and the state of the art in gene suppression using interfering RNA, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the

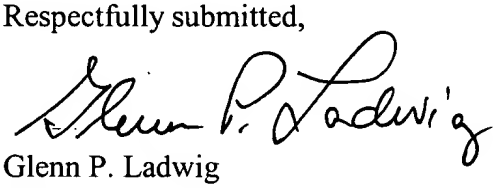
foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Declaration under 37 CFR § 1.132 by Dr. Kerr, with Exhibits A-I